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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/888,309	06/21/2001	Melissa K. Carpenter	090/002	9525

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EXAMINER	
FALK, ANNE MARIE	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 09/21/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/888,309	CARPENTER ET AL.	
	Examiner	Art Unit	
	Anne-Marie Falk, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 July 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *23-47* is/are pending in the application.

4a) Of the above claim(s) *23-33 and 47* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *34-46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *21 June 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

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DETAILED ACTION

A request for continued examination under 37 CFR 1.114 was filed July 12, 2005.

The remarks filed March 17, 2005 (hereinafter referred to as "the response") are considered herein.

Claims 23-47 remain pending in the instant application.

Claims 23-33 and 47 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention. Applicant timely traversed the restriction requirement in the reply filed on November 6, 2003.

Accordingly, Claims 34-46 are examined herein.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114 was filed in this application after appeal to the Board of Patent Appeals and Interferences, but prior to a decision on the appeal. Since this application is eligible for continued examination under 37 CFR 1.114 and the fee set forth in 37 CFR 1.17(e) has been timely paid, the appeal has been withdrawn pursuant to 37 CFR 1.114 and prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on March 17, 2005 was entered as set forth in the Advisory Action of April 12, 2005.

Priority

Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed applications, Application Nos. 60/213,740, 60/213,739, 60/216,387, and 60/220,064, fail to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application. The prior-filed applications fail to satisfy the requirements of 35 U.S.C. 112, first paragraph for the same reasons discussed herein with respect to the instant specification.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

New Matter/Written Description

Claims 34-46 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the claimed invention. Applicants are referred to the final guidelines on written description published January 5, 2001 in the Federal Register at Volume 66, Number 4, pp. 1099-1111 (also available at www.uspto.gov). The rejection is reiterated below.

The claims recite combinations without support in the original disclosure, thereby adding new matter to the claims.

The claims recite **a system comprising two cell populations or a plurality of cell populations.** Claim 34 is directed to a system for producing differentiated cells from human embryonic stem (hES) cells, consisting of:

a first cell population comprising undifferentiated hES cells; and

a second cell population comprising progeny of the hES cells in a medium containing one or more added TGF-β superfamily antagonists.

Claim 35 is directed to a plurality of cell populations cultured during production of tyrosine hydroxylase positive neuronal cells from a line of hES cells, comprising:

said line of undifferentiated hES cells; and

a second cell population, comprising at least ~10% hES-derived neural cells, identifiable by the criteria that they are progeny of said hES cells and express both MAP-2 and tyrosine hydroxylase. However, the claims are not supported by the original disclosure because the original disclosure does not specifically contemplate this combination of two cell populations. At page 5 of the preliminary amendment (filed 11/6/03), Applicants refer to page 4, lines 34-35 of the specification as providing support for the new claims. The cited lines read "[t]his invention provides a system for efficient production of differentiated cells from primate pluripotent stem (pPS) cells." However, this section only provides support for certain elements of the claims and does not provide specific support for the **combination of two cell populations** now being claimed. The Examiner has carefully reviewed the entire specification and does not find support for the claimed invention as a whole. Applicants have not pointed to specific support for the claims in the specification as-filed.

The **combination** of the two cell populations is not described in the specification and therefore constitutes new matter, for lack of written description.

Thus, the claims include new matter.

No new arguments are set forth regarding this rejection.

Enablement

Claims 34-46 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The rejection is reiterated below.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, are set forth in *In re Wands*, 8 USPQ2d 1400, at 1404 (CAFC 1988). These factors include: (1) the nature of the invention, (2) the state of the prior art, (3) the relative level of skill of those in the art, (4) the predictability of the art, (5) the breadth of the claims, (6) the amount of direction or guidance presented, (7) the presence or absence of working examples, and (8) the quantity of experimentation necessary.

The following factors have been considered.

Nature of the invention. The claims are directed to a system comprising two cell populations. As claimed, the two cell populations are intended to be used together somehow. However, the specification does not specifically disclose how to use these two cell populations together. The specification contemplates that the cells of the invention can be used in drug screening. However, the specification does not disclose how one would use the claimed **system of two cell populations** in drug screening. The specification also discloses that the cell populations are intended to be used for therapeutic transplantation (see the specification at page 24, lines 20-22). The specification states that "[c]ells prepared according to this invention that are useful for human or veterinary therapy are optimally supplied in a pharmaceutical composition ..." (page 25, lines 5-6). The specification contemplates using a variety of differentiated cell types, such as neural cells, cardiomyocytes, and hepatocytes, for therapeutic transplantation (page 24, lines 19-41). However, the specification does not address how to

use the **system of two** cell populations. As discussed above, the specification does not specifically contemplate a **system of two** cell populations as claimed.

Amount of direction or guidance presented and the presence or absence of working examples. The specification discloses in Example 5 the testing of various factors for use in the differentiation of hES cells to neurons. However, none of the examples demonstrate the use of the claimed **system of two cell populations.** As discussed above, the specification does not contemplate a **system of two** cell populations as claimed. Thus, the specification does not adequately teach how to use the claimed compositions. Furthermore, none of the examples demonstrate a therapeutic use of the system of two cell populations.

The specification contemplates using the various "differentiated cells of this invention" to screen candidate compounds or environmental conditions that affect differentiation or metabolism of a cell type of interest" (page 5, lines 36-37). Again however, the specification does not provide any guidance for using the claimed **system of two** cell populations in drug screening assays. The specification must provide specific guidance for the use of the **claimed** compositions. Here it does not.

It is not to be left up to the skilled artisan to figure out how to use the claimed compositions. The courts held that the disclosure of an application shall inform those skilled in the art how to use applicant's claimed invention, not how to **find out** how to use it for themselves. *In re Gardner et al.* 166 USPQ 138 (CCPA 1970). With regard to the differentiated cells described in the specification, this specification only teaches what is intended to be done and how it is intended to work, but does not actually teach how to do that which is intended. With regard to the **claimed** compositions, the specification does not provide any guidance for their use.

State of the prior art and predictability of the art. The state of the art is such that very little is known about the cell types that can be used to restore neurological function. One of the lingering questions in the field of stem cell research relates to the stage of differentiation of stem cells useful for

transplantation and whether the same stage will be useful for all transplantation applications, or vary on a case-by-case basis (see p. ES-8, column 1 of Stem Cells: Scientific Progress and Future Research Directions, June 2001).

In a review of the state of the art of stem cell technology, the National Institutes of Health acknowledge the potential usefulness of stem cells in theraeutic transplantation and the possible development of therapeutic protocols in the future (see Stem Cells: Scientific Progress and Future Research Directions, June 2001). However, the review also illustrates that there are numerous and significant obstacles that must be overcome. As such, the asserted utility of the present invention, directed to using the claimed compositions in therapeutic transplantation constitutes a credible utility, albeit one that is not enabled by the instant specification. The instant rejection therefore is not for lack of utility, but rather for lack of enablement for the asserted utility. Furthermore, the asserted utilities of therapeutic transplantation or drug screening are the only utilities disclosed for the differentiated cells referred to in the specification. However, the specification does not provide specific guidance for the use of the **claimed** compositions (the system of two cell populations). With regard to therapeutic transplantation, there is no teaching at all for using the claimed combinations of cell populations in therapeutic transplantation. With regard to drug screening, there is no teaching at all for using the claimed combinations of cell populations in drug screening assays. For the reasons discussed herein, the specification does not teach how to use the **claimed** compositions for the utilities contemplated for the **differentiated cells** referred to in the specification.

The specification fails to provide an enabling disclosure for using the claimed compositions in accordance with the utilities asserted in the specification for differentiated cells (*i.e.*, for drug screening or therapeutic transplantation). The utilities asserted in the specification are directed to uses for precursor cells and terminally differentiated cells, but not to the specific combination of cell populations instantly claimed.

The specification fails to provide an enabling disclosure for using the claimed compositions to provide a therapeutic benefit because the specification does not provide **specific guidance** regarding how to use the claimed compositions therapeutically. In unpredictable arts, it is the specification itself that must provide the novel teachings for using the claimed compositions therapeutically. The specification does not offer any guidance as to how the claimed compositions could be used therapeutically for the treatment of any disorder. No working examples demonstrate a therapeutic effect in a diseased animal upon transplantation of the claimed compositions. The specification contemplates that "cells of the invention" can be used therapeutically. Accordingly, the specification must teach how to use the claimed system or plurality of cell populations in transplantation protocols to produce a therapeutic effect. However, the specification does not teach how to produce a therapeutic effect in any animal. The specification fails to provide any guidance relating to the amount of cells to inject, the site of injection, and extent of cellular persistence required to provide any therapeutic benefit for any disorder. There are no teachings regarding the administration of the two separate cell populations recited in the claims. There is no guidance relating to the order of administration of the two cell populations, the physical location for implantation of each cell population, or the route of administration for the two cell populations, whether the same or different.

The court has recognized that physiological activity is unpredictable. *In re Fisher*, 166 USPQ 18 (CCPA 1970). In cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved. *In re Fisher*, 166 USPQ 18 (CCPA 1970).

Given the limited working examples, the limited guidance provided in the specification, the lack of any showing of therapeutic benefit upon transplantation of the claimed compositions, the lack of any use for the claimed compositions in drug screening assays, the broad scope of the claims, and the unpredictability for producing a therapeutic effect upon transplantation of the claimed compositions

(consisting of a system of two cell populations), undue experimentation would have been required for one skilled in the art to use the claimed compositions in methods of transplantation to produce a therapeutic effect or in drug screening assays.

No new arguments are provided with regard to this rejection.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 34-46 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 34 and 41-46 are indefinite in their recitation of the term "system" because the metes and bounds of the term are not clearly set forth.

At page 5 of the response, Applicants assert that the amendment to Claim 34 explicityly defines the scope of the claimed system by use of the phrase "consisting of." However, the "consisting of" claim language is followed by the open claim language "comprising" and "containing" and thereby negate the effect of the "consisting of" claim language (further discussed below). Furthermore, the claimed system comprises more than just two cell populations because it must also comprise a medium. According to the claim language, the medium can contain anything. Therefore, the "consisting of" claim language does not limit the scope of the claimed system. Thus, the scope of the claimed system is not defined by the amendment to the claim.

Claims 34 and 41-46 are indefinite in their recitation of "consisting of", which is closed claim language, followed by the terms "comprising" and "containing" which are open claim language. Thus, the "consisting of" claim language is negated by the "comprising" and "containing" claim language. The "consisting of" language is ineffective and therefore confusing. See *In re Crish*, 73 USPQ2d 1364 (CAFC 2004).

Claims 35-40 are indefinite in their recitation of "second cell population" because there is no recitation of a "first cell population."

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 34, 41, 45, and 46 are rejected under 35 U.S.C. 102(b) as being anticipated by Thomson et al. (1998; Science 282: 1145-1147) and Church et al. (May 1999; Calcified Tissue International 64 (Suppl. 1): S54).

Claim 34 is directed to a system for producing differentiated cells from human embryonic stem (hES) cells, consisting of:

a first cell population, comprising the undifferentiated hES cells; and

a second cell population, comprising progeny of the hES cells in a medium containing one or more added transforming growth factor β (TGF-β) superfamily antagonists.

Claim 41 is directed to the system of Claim 34, wherein the second cell population is in a medium containing noggin.

Claim 45 is directed to the system of Claim 34, wherein the second cell population has been obtained by a process comprising differentiating the hES cells by plating them onto a solid surface without forming embryoid bodies or cell aggregates.

Claim 46 is directed to the system of Claim 45, wherein the solid surface comprises fibronectin or a polycation.

Claim construction: The two cell populations are not related temporally or spatially. Applicants have acknowledged that the two cell populations need not co-exist at the same time, but rather may exist sequentially (paragraph 7 of the Declaration filed 5/27/04) and further that they need not co-exist in the same place (page 8, paragraph 3 of the response filed 5/27/04). For example, one cell population may be located in Los Angeles, while the other cell population is in New York City. The claimed "system" does not require that the two cell populations be in contact with each other (as a composition) or be packaged together as in a kit. Thus, when given their broadest reasonable interpretation, the claimed "system" encompasses two separate products known in the art at the time of filing. This is the equivalent of claiming a sofa and a cotton plant.

The phrase "progeny of the hES cells" is a product-by-process recitation and is given patentable weight insofar as it defines the structure implied by the process. See MPEP § 2113. Product-by-process claims are not limited to the manipulations of the recited steps, only the structure implied by the steps. The patentability of a product does not depend on its method of production. Thus, the claims read on cells disclosed in the prior art, as discussed below. Claims 45 and 46 recite further process steps for obtaining the second cell population by differentiating hES cells under certain conditions. However, the further process steps do not further limit the structure implied by the steps.

Thomson et al. (1998) discloses human embryonic stem cell lines derived from human blastocysts. The cell lines were maintained in the undifferentiated state over at least 5 to 6 months of culture. The human ES cell lines maintained the potential to form derivatives of all three embryonic germ layers (page 1146, column 1, paragraph 3).

Church et al. (May 1999) disclose the culture of human marrow mesenchymal stem cells in a medium containing noggin (a TGF-β superfamily antagonist). Since ES cells are responsible for producing cell types from all three germ layers (as evidenced by Thomson et al.), human marrow mesenchymal stem cells are necessarily the *in vivo* progeny of human ES cells.

Thus, the claimed invention is anticipated by Thomson et al. and Church et al.

Claims 34, 42, 45, and 46 are rejected under 35 U.S.C. 102(b) as being anticipated by Thomson et al. (1998; Science 282: 1145-1147) and Wang et al. (April 1999; J. of Urology 161: 13378-1384).

Claim 34 is directed to a system for producing differentiated cells from human embryonic stem (hES) cells, consisting of:

a first cell population, comprising the undifferentiated hES cells; and

a second cell population, comprising progeny of the hES cells in a medium containing one or more added transforming growth factor β (TGF-β) superfamily antagonists.

Claim 42 is directed to the system of Claim 34, wherein the second cell population is in a medium containing follistatin.

Claim 45 is directed to the system of Claim 34, wherein the second cell population has been obtained by a process comprising differentiating the hES cells by plating them onto a solid surface without forming embryoid bodies or cell aggregates.

Claim 46 is directed to the system of Claim 45, wherein the solid surface comprises fibronectin or a polycation.

Claim construction: The two cell populations are not related temporally or spatially. Applicants have acknowledged that the two cell populations need not co-exist at the same time, but rather may exist sequentially (paragraph 7 of the Declaration filed 5/27/04) and further that they need not co-exist in the same place (page 8, paragraph 3 of the response filed 5/27/04). For example, one cell population may be located in Los Angeles, while the other cell population is in New York City. The claimed "system" does not require that the two cell populations be in contact with each other (as a composition) or be packaged together as in a kit. Thus, when given their broadest reasonable

interpretation, the claimed "system" encompasses two separate products known in the art at the time of filing. This is the equivalent of claiming a sofa and a cotton plant.

The phrase "progeny of the hES cells" is a product-by-process recitation and is given patentable weight insofar as it defines the structure implied by the process. See MPEP § 2113. Product-by-process claims are not limited to the manipulations of the recited steps, only the structure implied by the steps. The patentability of a product does not depend on its method of production. Thus, the claims read on cells disclosed in the prior art, as discussed below. Claims 45 and 46 recite further process steps for obtaining the second cell population by differentiating hES cells under certain conditions. However, the further process steps do not further limit the structure implied by the steps.

Thomson et al. (1998) discloses human embryonic stem cell lines derived from human blastocysts. The cell lines were maintained in the undifferentiated state over at least 5 to 6 months of culture. The human ES cell lines maintained the potential to form derivatives of all three embryonic germ layers (page 1146, column 1, paragraph 3).

Wang et al. (April 1999) discloses primary cultures of human prostate epithelial cells in a medium comprising follistatin. See the paragraph bridging columns 1 and 2 on page 1379, which describes the culture of human prostate epithelial cells. See also Figure 2 and the legend to Figure 2. Since ES cells are responsible for producing cell types from all three germ layers (as evidenced by Thomson et al.), human prostate epithelial cells are necessarily the *in vivo* progeny of human ES cells.

Thus, the claimed invention is anticipated by Thomson et al. and Wang et al.

Conclusion

No claims are allowable.

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Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne-Marie Falk whose telephone number is (571) 272-0728. The examiner can normally be reached Monday through Friday from 10:30 AM to 7:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on (571) 272-0735. The central official fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Anne-Marie Falk, Ph.D.

Anne-Marie Falk

ANNE-MARIE FALK, PH.D
PRIMARY EXAMINER